UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,647	04/07/2004	Kevin Liu	063768-0309115	8504

7590 10/04/2007

Pillsbury Winthrop LLP
Intellectual Property Group
Suite 200
11682 El Camino Real
San Diego, CA 92130-2092

EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
10/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,647	LIU ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18-36,41-57 and 59-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *50 and 70* is/are allowed.

6)☒ Claim(s) *1-13, 18-36, 41-49, 51-57, 59-64, 65-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on July 16, 2007.

Claims 1-3, 18-36, 41-57 and 59-70 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 1-13, 18-36, 41-49, 51-56, 59-64 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula I or a pharmaceutically acceptable N-oxide or salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable **prodrug, metabolite, ester, amide** or **solvate** thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Specification has no working example of a **metabolite** or **solvate** of a compound of the various structural formulae of the instant claims. For example, some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds. Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'a patent

need not disclose what is well known in the art'.

MPEP 2164.03 provides the relationship of predictability of the art and the enablement requirement (portion of MPEP is provided below for convenience):

> **2164.03 [R-2] Relationship of Predictability of the Art and the Enablement Requirement**
>
> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification.
> **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).<
> **The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.** If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, **if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.** Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:
>
> > **[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim.** This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]
>
> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, **in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.** *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999

> F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). **This is because it is not obvious from the disclosure of one species, what other species will work.**

As explained in the previous office action, the specification or the state of the art provides all possible 'prodrug', 'metabolite', 'ester', 'amide' or 'solvate' forms of the compounds of formula (I). MPEP 2164.04 requires that - 'a reasonable basis to question the enablement of the claimed invention must be provided'. This was done by discussing state of the art references Bundgaard, West, Vippagunta, Ulrich, etc. (copies provided with the previous office action). Particularly, MPEP section provides:

> While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

Applicant indicates with regards to 'prodrug', 'ester' and 'amide' that 'specific working examples are not required to satisfy 35 USC 112, first paragraph'. With respect to 'metabolite', applicant argues that 'a person having ordinary skill in the art would recognize the pharmaceutically active metabolites of compounds of formula (I)'. However, there is no description of any such prodrugs or metabolites of the compound or a method of preparation of the same. The specification does not provide any explanation regarding how the instantly recited characteristic of a metabolite is established. There is neither a procedure describing how such metabolites are prepared nor examples that illustrate the recited activity. Further, the instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to a characteristic or functionality of the compound or composition and thereby reach through to all types of compositions, for which they lack written description and enabling disclosure in the

specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The state of the references provide the unpredictable nature pertinent to the scope of the instant claims, see e.g., West: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Vippagunta: "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Generally, 'solvate' is formed by the association or combination of a solute unit with solvent molecules which association may involve physical or chemical forces or both and may vary in degree from a loose, indefinite complex to the formation of a distinct chemical compound. A recent state of the art reference, Peterson et al. (J Pharm Pharmaceut Sci 2006) provides 'solvate' as a type of crystal form of pharmaceutical compounds (see page 317). The reference further provides the challenges associated with the design of crystalline materials that include one or more solvent/water molecules in the crystal lattice. "By extension, and just as the exact function of a protein and quantitative parameters of activity are not predictable from primary and secondary structure, the prediction of crystal properties is not possible in the absence of structural information and measurements"; "even when chemically compatible functional groups are present it is not possible to accurately predict if a co-crystal, a eutectic mixture or simply a physical mixture will result from any given experiment" (see page 320, col. 2). "There remain several limitations to the applications of what is currently known to the design of useful materials. As mentioned earlier, it remains intractable to reliably predict crystal structure. Multi-component crystals are well out of reach for prediction due in part to complex

energetic landscapes, lack of appropriate charge density models and a large number of degrees of freedom, making computation unfeasible" (see page 322, col. 1). The reference further identifies 'the challenges faced by pharmaceutical scientists' as: "(i) to understand the requirement of a particular compound in terms of materials structure and properties, and (ii) to creatively integrate crystal engineering within the limits of pharmaceutical acceptability of components to obtain new forms of active ingredients with desirable properties for formulation and delivery" (see page 322, col. 2).

As per the collective discussion provided in the previous and present office actions, it is established that the fact situation based on the disclosure and the state of the art references, fails to teach how to make and use the instant invention commensurate in scope of the claims, without undue experimentation.

2. Claims 51-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of diabetes, does not reasonably provide enablement for a method of modulating a peroxisome proliferators-activated receptor (PPAR) function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant argues that 'exemplified compounds were evaluated in a cell-based assay to determine their human PPAR activity and results are disclosed on pages 48-51 of the

specification' and 'because the PPAR binding activity can be determined through routine experimentation, a person having skill in the art has no need to be able to predict activity based on structure in order to practice the claimed invention'. However, it was clearly indicated in the previous office action the unpredictability of therapeutic approach related to many of the diseases encompassed by the instant claims and applicant did not provide any explanation as to how treatment of all types of PPAR induced diseases is enabled. Further, one skilled in the art recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to various disease states, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases induced by PPAR.

Applicant's arguments with regards to claims reciting 'method of treating PPAR-modulated diseases' and 'a method of treating a disease selected from the group consisting of obesity, diabetes, ... and hypertoxic lung injury' have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides and solvates; a method of modulating a PPAR function; a method of treating a PPAR-modulated disease; etc.'. However, the biological data in pages 48-51 provides a range of EC_{50} data for the instant compounds with respect to PPAR-binding activity and there is nothing in the specification how this data extrapolates to the treatment of all types of specific diseases, e.g., metabolic disorders, etc. of the instant claims. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders encompassed by the claims. As can be seen from specification, the *in vitro* biological data holds

significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired activity.

Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule for treatment of any particular disease. A detailed understanding of the molecular mode of action of the PPAR alongside the elucidation of the molecular pathology of individual disease is required to identify the disease symptoms and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters for each individual disease therapeutic intervention.

There is no evidence of record, which would enable the skilled artisan in the identification of the patient that is in need of the instantly claimed therapeutic activity. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the treatment of the diverse disorders instantly claimed.

Allowable Subject Matter

Claims 50 and 70 are allowed. The references of record do not teach or fairly suggest the instantly claimed compound.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

October 1, 2007